REMARKS/ARGUMENTS

Claims 28-35, 38-40, and 44-52 are pending in this application.

Applicants note and appreciate the withdrawal of the earlier objections and rejections under 35 U.S.C. §101, 35 U.S.C. §102, and 35 U.S.C. §112, first paragraph, for scope of enablement. Applicants also appreciate the allowance of claims 33-35 and 38-40. The remaining rejections of claims 28-32 and 44-52 under 35 U.S.C. §112, first paragraph, are addressed below.

I. Claim Rejections Under 35 U.S.C. §112 - Written Description

Claims 28-32 and 44-52 are rejected under 35 U.S.C. §112, first paragraph, as allegedly containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention. The Examiner asserts that "the genus includes variants for which no written description is provided in the specification. This large genus is represented in the specification by only the particularly named SEQ ID NO:219. Thus, applicant has express possession of only one particular nucleic acid sequence in a genus which comprises hundreds of millions of different possibilities. Here, no common element or attributes of the sequences are disclosed, not even the presence of certain domains." (Page 3 of the instant Office Action).

Applicants respectfully disagree and traverse the rejection.

The Legal Test for Written Description

The well-established test for sufficiency of support under the written description requirement of 35 U.S.C. §112, first paragraph is "whether the disclosure of the application as originally filed reasonably conveys to the artisan that the inventor had possession at that time of the later claimed subject matter, rather than the presence or absence of literal support in the specification for the claim language."[1] [2] The adequacy of written description support is a factual

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[1] *In re Kaslow*, 707 F.2d 1366, 1374, 212 USPQ 1089, 1096 (Fed. Cir. 1983).

[2] *See also Vas-Cath, Inc. v. Mahurkar*, 935 F.2d at 1563, 19 USPQ2d at 1116 (Fed. Cir. 1991).

issue and is to be determined on a case-by-case basis.[3] The factual determination in a written description analysis depends on the nature of the invention and the amount of knowledge imparted to those skilled in the art by the disclosure. [4] [5]

In *Environmental Designs, Ltd. v. Union Oil Co.*,[6] , the Federal Circuit held, "Factors that may be considered in determining level of ordinary skill in the art include (1) the educational level of the inventor; (2) type of problems encountered in the art; (3) prior art solutions to those problems; (4) rapidity with which innovations are made; (5) sophistication of the technology; and (6) educational level of active workers in the field." (Emphasis added).[7] Further, The "hypothetical 'person having ordinary skill in the art' to which the claimed subject matter pertains would, of necessity have the capability of understanding the scientific and engineering principles applicable to the pertinent art."[8] [9]

The Disclosure Provides Sufficient Written Description for the Claimed Invention

Applicants first respectfully maintain the position that that Claims 28-32 and 44-52 satisfy the written description requirement under 35 U.S.C. §112, first paragraph, for the reasons previously set forth in Applicants' Response filed on November 8, 2004.

Applicants next respectfully submit that the instant specification evidences the actual reduction to practice of a full-length PRO1780 polypeptide of SEQ ID NO:220, with or without its signal sequence. The Examiner has acknowledged that polynucleotides encoding a

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[3] *See e.g., Vas-Cath*, 935 F.2d at 1563; 19 USPQ2d at 1116.

[4] *Union Oil v. Atlantic Richfield Co.*, 208 F.2d 989, 996 (Fed. Cir. 2000).

[5] *See also* M.P.E.P. §2163 II(A).

[6] 713 F.2d 693, 696, 218 USPQ 865, 868 (Fed. Cir. 1983), *cert. denied*, 464 U.S. 1043 (1984).

[7] *See also* M.P.E.P. §2141.03.

[8] *Ex parte Hiyamizu*, 10 USPQ2d 1393, 1394 (Bd. Pat. App. & Inter. 1988) (emphasis added).

[9] See *also* M.P.E.P. §2141.03.

polypeptide comprising the sequence set forth in SEQ ID NO:220 (as in Claims 33-35) meets the written description provision of 35 U.S.C. §112, first paragraph. Thus, the genus of polynucleotides that encode polypeptides with at least 80% sequence identity to SEQ ID NO:220, which possess the functional property of either inducing proliferation of kidney mesangial cells, or inducing proliferation of pancreatic β-cell precursor cells, would meet the requirement of 35 U.S.C. §112, first paragraph, as providing adequate written description.

Applicants have provided native PRO sequence SEQ ID NO:220, and SEQ ID NO:219 which encodes it. The present application also describes methods for identifying proteins which induce proliferation of kidney mesangial cells or pancreatic β-cell precursor cells. Example 145 of the present application provides step-by-step guidelines and protocols for the mouse kidney mesangial cell proliferation assay. By following the disclosure in the specification, one skilled in the art can easily test whether a polypeptide encoded by a variant PRO1780 polynucleotide induces proliferation of kidney mesangial cells. Example 151 of the present application provides step-by-step guidelines and protocols for the pancreatic β-cell precursor proliferation assay. By following the disclosure in the specification, one skilled in the art can easily test whether a polypeptide encoded by a variant PRO1780 polynucleotide induces proliferation of pancreatic β-cell precursor cells.

The specification also describes methods for the determination of percent identity between two amino acid sequences. (See page 302, line 4 to page 305, line 4). In fact, the specification teaches specific parameters to be associated with the term "percent identity" as applied to the present invention. The specification further provides detailed guidance as to changes that may be made to a PRO polypeptide without adversely affecting its activity (page 354, line 30 to page 357, line 7). This guidance includes a listing of exemplary and preferred substitutions for each of the twenty naturally occurring amino acids (Table 6, page 356). Accordingly, one of skill in the art could identify whether a variant PRO1780 polynucleotide sequence falls within the parameters of the claimed invention.

Accordingly, the specification provides adequate written description for polynucleotides encoding polypeptides having at least 80% identity to SEQ ID NO:220 wherein the encoded

polypeptide induces proliferation of kidney mesangial cells, or induces proliferation of pancreatic β-cell precursor cells.

The Examiner asserts,

> It is the absence of any real structure function relationship and the absence of a representative number of species which supports the conclusion that there is insufficient descriptive support for the current claims. This argument rests on several grounds. First, the single sequence that is actually described is not representative of the genus of any sequence which hybridizes under the claimed conditions. Second, the claims entirely lack a structure function relationship since the function given has no ability to limit the genus of polypeptides. Third, the claim encompasses species other than human.

(Page 6 of the instant Office Action).

Applicants respectfully point out that the claims are not directed to hybridizing sequences. The claims recite polynucleotides defined as encoding polypeptides having a specified degree of sequence identity to SEQ ID NO:220, as well as a specified function. Thus the Examiner's first point is not relevant to the claims at issue. Regarding the second point, Applicants respectfully note that the claims are directed to polynucleotides, not polypeptides.

The Examiner further asserts that the genus of polypeptides encoded by the claimed polynucleotides allegedly "represents every possible variation which could occur in SEQ ID NO:220, that has 80% identity," and that this genus includes 4^{120} sequences. This statement is incorrect. The claimed genus of polynucleotides includes only those encoding polypeptide variants having at least 80% identity to SEQ ID NO:220 which <u>also</u> have a specified activity, that is, inducing proliferation of kidney mesangial cells, or inducing proliferation of pancreatic β-cell precursor cells.

The Examiner asserts that the recited function allegedly "provides absolutely no guidance or information regarding the structure and does not limit the structure in even the smallest or most miniscule possible way." (Page 7 of the instant Office Action). Applicants respectfully disagree. First, the functional limitation clearly limits the structure of the variants in the obvious sense that a protein lacking any structural similarity with SEQ ID NO:220 would not be expected to conserve the same function. Second, it is not necessary that the functional limitation be directly linked to structure, because the claims <u>already</u> provide a structural limitation, in requiring that the polypeptide variants encoded by the claimed polynucleotides have at least 80%

amino acid sequence identity to SEQ ID NO:220. Given the correlation between the sequence of a protein and that of its encoding nucleic acid, the structural limitation to the encoded protein sequences amounts to a structural limitation to the claimed polynucleotides which encode the protein sequences. Applicants recognize that there may be polypeptides that induce proliferation of kidney mesangial cells or pancreatic β-cell precursor cells through mechanisms unrelated to those of PRO1780, and thus do not resemble PRO1780 in structure. These structurally unrelated polypeptides, however, would not be encompassed by claims requiring at least 80% amino acid sequence identity to SEQ ID NO:220. Applicants claim only those polynucleotides which encode proteins meeting both limitations of the claims, structural and functional. Given the structural limitation, the additional functional limitation clearly acts to further define the claimed genus.

As the Examiner points out, the size of the genus is a central issue, because if the genus were smaller, a written description issue would be less likely, since the examples would be more representative of the genus. As discussed above, the claims do not encompass anywhere near the extremely large number of species stated in the Office Action, because the Examiner's calculation is based solely upon the structural limitation of at least 80% sequence identity. Once the additional functional limitations are included, the genus is limited to a size where the demonstrated species suffices to represent the genus.

The Office Action appears to interpret the quoted statement in *The Regents of the University of California v. Eli Lilly and Co.* (43 U.S.P.Q.2d 1398 (Fed. Cir. 1997)) that a definition by function does not suffice to define a genus, as meaning that functional limitations are without significance, and may be ignored. Applicants do not, as in *Lilly*, claim polynucleotide sequences solely by their functional utility or expected result. Rather, the recited functional limitations serve to supplement the recited structural limitations. Furthermore, the recited functional limitations do not set forth only a "useful result," but the features which achieve that result, as required by *Lilly*. The claims do not recite proteins of unspecified characteristics that are useful in treating kidney diseases or disorders associated with decreased β-cell function, such as diabetes mellitus. The claims recite proteins which have a specific

activity, inducing proliferation of kidney mesangial cells or pancreatic β-cell precursor cells, which can be measured by assays disclosed within the specification.

The Office Action also appears to argue that Applicants must provide a single limitation that describes both structural and functional attributes together, asserting that the Written Description Guidelines "require a structure function relationship." (Page 8 of the instant Office Action). The Office Action fails to explain where this requirement is found in the Written Description Guidelines. Applicants respectfully note that there is no "structure function relationship" provided in Example 9 of the Written Description Guidlines. Rather, the claims in Example 9 resemble the instant claims in providing both a structural limitation (given that polynucleotides which hybridize to the reference sequence under stringent conditions would share significant sequence identity), together with a separate functional limitation, that the encoded polypeptides have adenylate cyclase activity. Since the structural limitation pertains to the polynucleotides, while the functional limitation pertains to the encoded polypeptides, it is difficult to see how there can be a direct structure function relationship.

The Examiner's attention is respectfully directed to Example 14 of the Synopsis of Application of Written Description Guidelines issued by the U.S. Patent Office, which clearly states that protein variants meet the requirements of 35 U.S.C. §112, first paragraph, as providing adequate written description for the claimed invention even if the specification contemplates but does not exemplify variants of the protein if (1) the procedures for making such variant proteins are routine in the art, (2) the specification provides an assay for detecting the functional activity of the protein and (3) the variant proteins possess the specified functional activity and at least 95% sequence identity to the reference sequence.

As discussed above, the procedures for making the recited variant proteins are well known in the art and described in the specification. The specification also provides assays, shown in Example 145 and Example 151, for detecting the specified functional activity of the recited variants. Finally, the recited variant proteins possess both the specified functional activity and a defined degree of sequence identity to the reference sequence, SEQ ID NO:220. Accordingly, the recited variants, and the claimed polynucleotides that encode them, meet the standards set forth in the Written Description Guidelines.

Finally, the Examiner asserts that Applicants' claims suffer from the same flaw as in *Lilly*, since the instant claims would allegedly encompass sequences from other species. Applicants respectfully point out that the issue is not whether the claims encompass sequences from other species, but whether the claimed sequences are adequately described. The assumption that any claim which covers sequences from another species is automatically too broad would lead to the perverse result that a genus that was more highly conserved across species would be harder to provide written description for, since any given degree of sequence identity would be more likely to include the variants from other species.

As discussed above, the claimed sequences are defined both by a structural limitation (encoding proteins having at least 80% amino acid sequence identity to a described reference sequence), and by a functional limitation, (encoding proteins having a specific biological activity, as measured by specific, disclosed assays). This biological activity, coupled with a well defined, and relatively high degree of sequence identity, sufficiently defines the claimed genus, such that one skilled in the art would readily recognize that the Applicants were in the possession of the invention claimed at the effective filing date of this application.

For the above-noted reasons, Applicants respectfully request the Examiner to reconsider and withdraw the written description rejections under 35 U.S.C. §112, first paragraph.

CONCLUSION

All claims pending in the present application are believed to be in *prima facie* condition for allowance, and an early action to that effect is respectfully solicited.

In the event that this office action is not entered or does not result in an allowance of the application, applicants file herewith a Notice of Appeal (attached).

Please charge any additional fees, including any fees for additional extension of time, or credit overpayment to Deposit Account No. **08-1641**, referencing Attorney's Docket No. **39780-2830 P1C54**). Please direct any calls in connection with this application to the undersigned at the number provided below.

Respectfully submitted,

Date: July 15, 2005

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